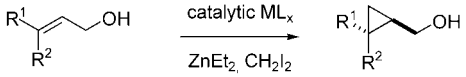
Cyclopropanations

Enantioselective Organocatalytic Cyclopropanation via Ammonium Ylides**

*Charles D. Papageorgiou, Maria A. Cubillo de Dios, Steven V. Ley, and Matthew J. Gaunt**

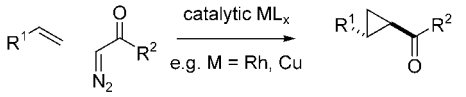
The cyclopropane motif is a common feature in the synthesis of complex molecules and in medicinal chemistry owing to a unique combination of reactivity and structural properties.[1] These properties have made the preparation of cyclopropanes an attractive target for new methodology development. Despite the many processes for the synthesis of functionalized cyclopropanes, there are surprisingly few general catalytic enantioselective methods.[2] Of the methods available, the carbenoid-mediated reactions[2c–e] are most often utilized [Eqs. (1,2)]; however, there are isolated examples of catalytic-ylide-based enantioselective cyclopropanations.[2a,b,e]

Lewis Acid Catalysis: Simmons-Smith type cyclopropanation



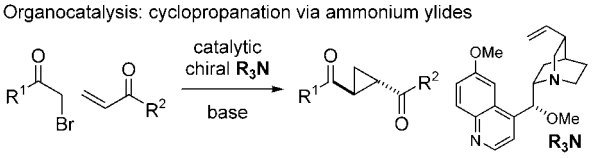
(1)

Metal Catalysis: metallocarbenoid-mediated cyclopropanation



(2)

Organocatalysis: cyclopropanation via ammonium ylides

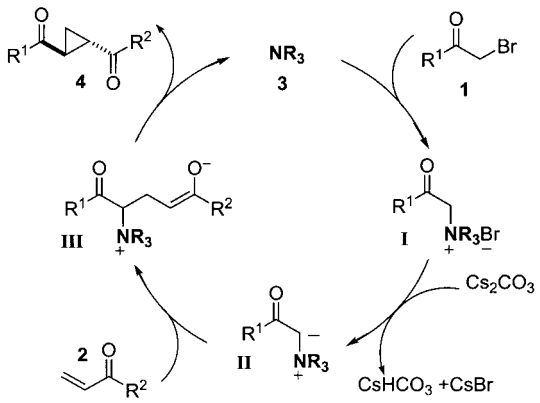


(3)

Recently, we described a cyclopropanation process with a reaction that was mediated by a stoichiometric quantity of a nucleophilic tertiary amine through the formation of an ammonium ylide.[3] We also developed an intramolecular version of this reaction that forms [*n*.1.0]bicyloalkanes as single diastereomers.[3b] Herein, we report the evolution of our studies and the resulting development of a general and practical intermolecular enantioselective organocatalytic cyclopropanation reaction via ammonium ylides. This process produces a range of functionalized molecules with excellent diastereo- and enantioselectivity and as either enantiomer [Eq. (3)].

This enantioselective catalytic cyclopropanation process via ammonium ylides[4] has a number of advantages over its counterparts: There are no transition metals involved in the reaction, and the starting materials are readily available and conveniently handled.[5] Furthermore, the number of known chiral amines represents a significant pool from which potential catalysts can be selected.

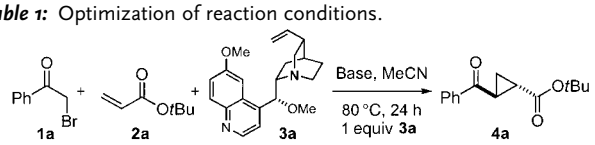
In this system, an α-bromo carbonyl compound **1** undergoes S_N2 displacement with the tertiary amine catalyst **3** to form a quaternary ammonium salt **I**. Deprotonation with mild base forms the ylide **II**, which undergoes conjugate addition to alkene **2** to form **III**. Finally, *3-exo-tet* cyclization generates the cyclopropane **4** and reforms the catalyst (Scheme 1).



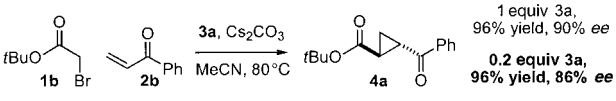
Scheme 1. Proposed catalytic cycle.

To assess the viability of this intermolecular process, reaction conditions were investigated with phenacyl bromide (**1a**), acrylate **2a**, and a stoichiometric quantity of quinine derivative **3a** (Table 1). By screening bases it became apparent that the larger the metal cation (Na→Cs), the better the yield of cyclopropane **4a**, although the enantioselectivity was lower. However, reversing the role of the starting

Table 1: Optimization of reaction conditions.



Entry	Base	Yield [%]	*ee* [%]
1	NaOH	**58**	**94**
2	Na_2CO_3	**19**	**96**
3	Na_2CO_3, [15]crown-5	**57**	**86**
4	K_2CO_3	**61**	**86**
5	Rb_2CO_3	**77**	**74**
6	Cs_2CO_3	**84**	**71**



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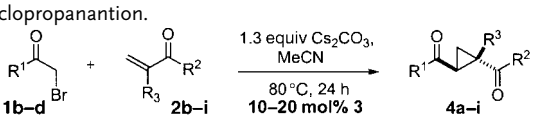
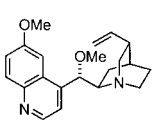
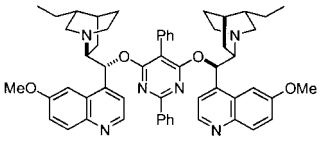
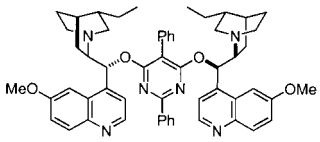
materials so that *tert*-butyl bromoacetate (**1b**) reacted with phenyl enone **2b** in the presence of **3a** resulted in a dramatic change to the outcome of the reaction: cyclopropane **4a** was isolated in 96% yield with 90% *ee* when 1 equivalent of **3a** was used. Most importantly, when the amount of tertiary amine was decreased to 0.2 equivalents, the reaction produced the cyclopropane **4a** in 96% yield with 86% *ee* (same enantiomer as Table 1, entry 6).[6]

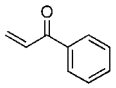
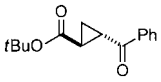
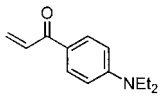
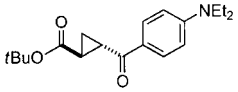
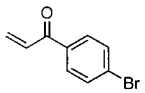
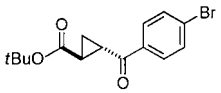
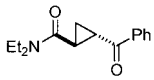
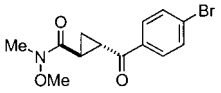
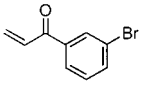
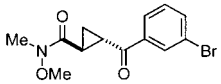
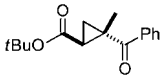
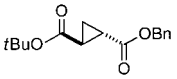
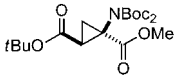
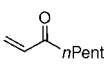
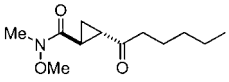
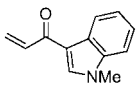
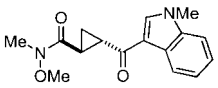
Table 2: Enantioselective organocatalytic cyclopropanantion.




3b


3c


3d

Entry[a]	R^1	Alkene		Product[b]		Catalyst	Yield [%]	*ee* [%]
1	O*t*Bu (**1b**)		**2b**		**4a**	**3a** **3b**	96 92	86 (+) 88 (−)
2	O*t*Bu (**1b**)		**2c**		**4b**	**3a** **3b**	73 73	84 (+) 84 (−)
3	O*t*Bu (**1b**)		**2d**		**4c**	**3a**	83	85 (+)
4	NEt_2 (**1c**)		**2b**		**4d**	**3a** **3b**	94 85	97 (+) 97 (−)
5	NMe(OMe) (**1d**)		**2d**		**4e**	**3c** **3d**	67 74	96 (+) 97 (−)
6	NMe(OMe) (**1d**)		**2e**		**4f**	**3c** **3d**	60 60	96 (+) 97 (−)
7	O*t*Bu (**1b**)		**2f**		**4g**	**3a**	63	92 (+)
8	O*t*Bu (**1b**)		**2g**		**4h**	**3a**	75	80 (+)
9	O*t*Bu (**1b**)		**2h**		**4i**	**3a** **3d** **3a**	90 83 53[c]	97 (+) 90 (−) 96 (+)
10	NMe(OMe) (**1d**)		**2i**		**4j**	**3a** **3d**	65 77	96 (+) 92 (−)
11[d]	NMe(OMe) (**1d**)		**2j**		**4k**	**3c** **3d**	74 84	95 (+) 94 (−)

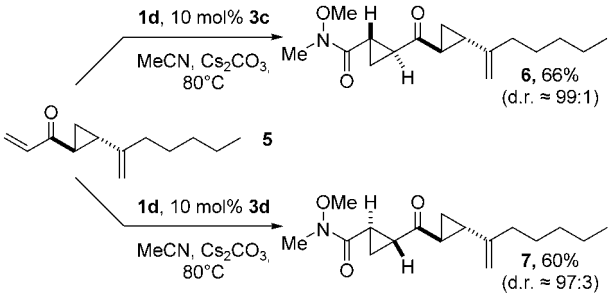
[a] **1** (1 equiv) and **2** (1.1 equiv) were added to Cs_2CO_3 and **3** (20 mol%) in MeCN (0.25 M) and stirred at 80 °C for 24 h. [b] (+)-enantiomer shown. [c] **3a**: 1 mol%. [d] **1d**: 2 equiv. Boc = *tert*-butoxycarbonyl.

Having identified an asymmetric process, its scope was investigated with the aim of producing a general catalytic enantioselective cyclopropanation reaction. Table 2 shows the range of cyclopropanes that can be formed by this method. A range of readily available cinchona alkaloids catalyzed the reaction. Importantly, both enantiomers of the cyclopropanes can be accessed in excellent yield and enantioselectivity by using either of the pseudoenantiomeric quinine or quinidine derivatives.[7] Interestingly, the use of alkaloid derivatives **3c** and **3d**[7] (10 mol%) often gave improved yield and enantioselectivity when **3a** or **3b** failed to give good results.

Bromoacetate **1b** reacts with a range of aryl vinyl ketones to form cyclopropanes **4a–c** in good yield and with excellent *ee* in the presence of 20 mol% of catalyst **3a**. The opposite enantiomer is also accessible by using the quinidine-derived catalyst **3b** (Table 2, entries 1–3). The role of these catalysts in the stereochemical outcome of the reaction is currently under investigation. It was also noticed that in some cases the slow addition of **1** and **2** to a solution of the catalyst resulted in higher yields. Changing the bromoacetate reagent **1b** to acetamide **1c** in the reaction with enone **2b** gave cyclopropane **4d** in excellent yield with 93% *ee*. The more versatile Weinreb amide derivative **1d** also produces the cyclopropanes with excellent *ee* values for **4e–f**.[8] High levels of substitution can be incorporated into the cyclopropane by using disubstituted enones or acrylates. For example, trisubstituted cyclopropane **4g** is produced in good yield and with high enantioselectivity. Aminocyclopropane **4i** was also formed in excellent yield and enantioselectivity, thus reflects the power of this process, which generates a high level of functionalization and stereocontrol on the cyclopropane core. The catalyst loading could also be lowered to 1 mol%, producing cyclopropane **4i** in 53% yield (53 catalyst turnovers) after 48 h without compromising the enantioselectivity. Cyclopropanation with bromomethyl alkyl ketones (**1**; R^1 = alkyl) was problematic and produced the cyclopropane in low yields. However, the application of the alkyl-substituted enones, such as **2i**, alleviated this problem, furnishing **4j** in excellent yield and enantioselectivity. Finally, the indole-derived cyclopropane **4k** was formed in good yield and with very high *ee* values, demonstrating the suitability of the reaction for the preparation of medicinally relevant compounds. To the best of our knowledge these results represent the first general intermolecular enantioselective organocatalytic cyclopropanation reaction.

Although it was not possible to form diketocyclopropanes directly by using the described method, they were accessible from the amide **4j**.[6] Thus, enone **5** could be readily generated and subjected to a second cyclopropanation reaction to form structurally and functionally complex biscyclopropanes **6** and **7** through reaction with **1d** (Scheme 2). Interestingly, catalyst **3c** produced **6** as a single diastereomer (d.r. ≈99:1), whereas catalyst **3d** gave only **7** (d.r. 97:3), suggesting that the stereoselectivity is controlled completely by the catalyst.

In summary, we have developed a new enantioselective organocatalytic cyclopropanation reaction. Importantly, the cyclopropanes can be produced as either enantiomer by using the quinine or quinidine series of cinchona alkaloid catalysts. The reaction is applicable to a range of substrates with a variety of versatile functional groups. We are currently investigating expansion of the scope of the reaction and applications to the synthesis of natural and non-natural products.



Scheme 2. Synthesis of biscyclopropanes.

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Keywords: asymmetric synthesis · cyclopropanation · nitrogen heterocycles · organocatalysis · ylides

[1] a) H.-U. Reissig, R. Zimmer, *Chem. Rev.* **2003**, *103*, 1151; b) J. Pietruszka, *Chem. Rev.* **2003**, *103*, 1051; c) W. A. Donaldson, *Tetrahedron* **2001**, *57*, 8589.

[2] For examples of asymmetric ylide-mediated cyclopropanation reactions, see: a) V. K. Aggarwal, E. Alonso, G. Fang, M. Ferrara, G. Hynd, M. Porcelloni, *Angew. Chem.* **2001**, *113*, 1482; *Angew. Chem. Int. Ed.* **2001**, *40*, 1433; b) W.-W. Lioa, K. Li, Y. Tang, *J. Am. Chem. Soc.* **2003**, *125*, 13030; for examples of carbenoid-mediated processes, see: c) S. E. Denmark, S. P. O'Connor, S. R. Wilson, *Angew. Chem.* **1998**, *110*, 1162; *Angew. Chem. Int. Ed.* **1998**, *37*, 1149, and references therein; d) A. B. Charette, C. Molinaro, C. Brochu, *J. Am. Chem. Soc.* **2001**, *123*, 12168; e) for a review, see: H. Lebel, J.-F. Marcoux, C. Molinaro, A. B. Charette, *Chem. Rev.* **2003**, *103*, 977.

[3] a) C. D. Papageorgiou, S. V. Ley, M. J. Gaunt, *Angew. Chem.* **2003**, *115*, 852; *Angew. Chem. Int. Ed.* **2003**, *42*, 828; b) N. Bremeyer, S. C. Smith, S. V. Ley, M. J. Gaunt, *Angew. Chem.* **2004**, *116*, 2735; *Angew. Chem. Int. Ed.* **2004**, *43*, 2681.

[4] a) S. S. Bhattacargee, H. Ila, H. Junjappa, *Synthesis* **1982**, 301; b) A. Jonczyk, A. Konarska, *Synlett* **1999**, 1085.

[5] a) P. I. Dalko, L. Moisan, *Angew. Chem.* **2001**, *113*, 3840; *Angew. Chem. Int. Ed.* **2001**, *40*, 3726; b) S. P. Brown, M. P. Brochu, C. J. Sinz, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2003**, *125*, 10800; c) P. Chandrakala, H. Linh, N. Vignola, B. List, *Angew. Chem.* **2003**, *115*, 2891; *Angew. Chem. Int. Ed.* **2003**, *42*, 2785, and references therein.

[6] See Supporting Information for full experimental information relating to stereochemical assignment and the determination of *ee* values. General experimental procedure: One-pot method: The catalyst **3a**, **3b** (0.2 equiv) or **3c**, **3d** (0.1 equiv), was added to a solution of the α-bromo carbonyl compound (1.0 equiv), the alkene (1.2 equiv), and Cs_2CO_3 (1.2 equiv) in MeCN (0.25 M) and stirred at 80 °C for 24 h. The reaction was quenched with aqueous HCl (1 M) and extracted three times with Et_2O or EtOAc. The combined organic phases were washed with a saturated aqueous solution of $NaHCO_3$, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash column chromatography. Slow addition method: A solution of the α-bromo carbonyl compound (1.0 equiv) and the alkene (1.2 equiv) in MeCN (0.25 M with respect to the α-bromo carbonyl com-

pound) was added to a solution of the catalyst **3a**, **3b** (0.2 equiv) or **3c**, **3d** (0.1 equiv) and Cs_2CO_3 (1.2 equiv) in MeCN (0.25 M) at 80 °C over 20 h by means of a syringe pump. The syringe was rinsed with MeCN and the reaction mixture stirred for a further 4 h. The reaction was quenched with aqueous HCl (1M) and extracted three times with Et_2O or EtOAc. The combined organic phases were washed with a saturated aqueous solution of $NaHCO_3$, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash column chromatography.

[7] For a recent review, see: S. France, D. J. Guerin, S. J. Miller, T. Leckta, *Chem. Rev.* **2003**, *103*, 2985.

[8] The amide derivatives **1c–d** give higher enantioselectivities (5–10%) than reactions with **1b**, although the yields are slightly lower (10–20%).

